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EDITORIAL

The creatinine conundrum in heart failure: rethinking AKI definitions

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Description of the problem

Acute heart failure (HF) is a leading diagnosis in the intensive care unit (ICU), accounting for nearly 40% of cardiac ICU admissions and associated with in-hospital mortality approaching 20% [1]. Congestion is a major driver of acute kidney injury (AKI) in this population and is increasingly recognized as a contributor to AKI in other critical illness settings, including sepsis and ARDS. Accurate interpretation of kidney function changes is therefore essential for optimizing ICU care. In this context, the rise in serum creatinine (RSC) seen in cardiorenal syndromes remains an ongoing diagnostic challenge. Serum creatinine is used to diagnose AKI, yet it reflects changes in glomerular filtration rather than structural injury. In HF, RSC often results from guideline-directed medical therapy (GDMT) or volume shifts and may not represent parenchymal damage. Applying the uniform threshold of KDIGO (≥0.3 mg/dL increase within 48 h) therefore risks misclassifying functional changes as injury and may lead to inappropriate modification of GDMT or decongestive strategies.

In patients admitted for acute HF, GDMT use at discharge strongly predicts long-term adherence, highlighting the importance of in-hospital initiation [2]. Current recommendations therefore support simultaneous or sequential initiation of GDMT during admission as the patient undergoes decongestion [3]. However, both GDMT and decongestion can modify serum creatinine, complicating interpretation. Importantly, improved outcomes in acute HF are driven primarily by GDMT initiation rather than decongestion alone [4, 5], which provides symptomatic relief without reducing mortality or rehospitalization [6].

RSC may reflect either benign functional adaptations during effective therapy or maladaptive responses due to persistent congestion. When RSC occurs alongside successful decongestion, it does not appear to worsen outcomes [7], whereas RSC in the presence of ongoing renal venous congestion portends poor prognosis [8]. Between these extremes, GDMT can also modify intraglomerular hemodynamics: RAAS inhibition induces efferent arteriolar vasodilation, while SGLT2 inhibitors enhance tubuloglomerular feedback with afferent vasoconstriction, both reducing glomerular hyperfiltration. These shifts typically produce modest (<0.3 mg/dL) RSC without tubular injury.

Although systematic biopsy data are lacking, single-center observations have shown largely preserved tubular morphology but marked dilation of renal veins and peritubular capillaries, consistent with congestion [9]. These findings suggest acute tubular necrosis is uncommon in HF, while chronic venous congestion may accelerate kidney fibrosis over time. This hypothesis, while intriguing, remains unproven in the absence of serial biopsy data.

Biomarker studies support this distinction. In the ROSE-AHF trial, "worsening renal function" (WRF) during decongestion—equivalent to KDIGO stage 1 AKI—was not associated with elevations in urinary tubular dysfunction/injury biomarkers (NAG, NGAL, or KIM-1) [10]. The most comprehensive evaluation to date, a secondary analysis of the AKINESIS study, reinforced these findings: among multiple cardiac and kidney biomarkers in patients with acute HF meeting KDIGO stage 1–2 AKI, only circulating galectin-3 predicted progression to higher WRF stage, dialysis, or death, whereas no urinary biomarker was associated with adverse renal outcomes [11]. Notably, in AKINESIS, BNP was not associated

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with adverse renal outcomes; however, a ≥ 30% reduction in BNP during hospitalization independently predicted one-year mortality [11, 12]. Circulating CA125 correlates more closely with renal venous congestion on Doppler than BNP [13], although its incremental value when combined with urinary biomarkers has not been established. Likewise, while urinary renal tubular epithelial cells are routinely assessed in clinical urinalysis and can indicate structural tubular injury [14], their evidence in acute HF and whether they provide additional value beyond existing biomarkers remains uncertain [15].

Applying the KDIGO threshold of 0.3 mg/dL is therefore problematic in HF. During titration of RAAS inhibitors, angiotensin receptor–neprilysin inhibitors, SGLT2 inhibitors, or diuretics, small RSC is common and should not automatically labeled as AKI. One of the earliest analyses exploring RSC in acute HF identified a rise ≥ 0.5 mg/dL as highly specific for predicting post-discharge mortality, conferring a two- to three-fold increase in the risk of death [16]. More recently, a renal Doppler study showed persistent renal venous congestion, associated with a ≥ 0.5 mg/dL increase in creatinine [8], was linked to higher rates of acute HF events and death at 30 days, further supporting this threshold as clinically meaningful in the context of congestion-related kidney dysfunction. Since large registries have shown that patients with acute HF do not have normal serum creatinine at baseline, applying the definition of KDIGO for AKI (1.5 times serum creatinine) will also point to a threshold higher than 0.3 mg/dL. However, context remains essential: in the SOLVD study, around one-third of patients initiating ACE inhibition experienced a creatinine rise ≥ 0.5 mg/dL, yet the survival benefits persisted even in advanced CKD (eGFR < 30 mL/min/1.73 m^2) [17]. Thus, even substantial RSC should not automatically be equated with harm when it accompanies effective GDMT or decongestion. Similarly, recent data suggest that effective decongestion is linked with better outcomes despite eGFR declines, unless eGFR decline exceeds 40% [18].

Available diagnostic tools for differential assessment

Because creatinine alone cannot distinguish between functional and structural AKI, complementary tools are essential. As outlined above, no tubular biomarker has yet proven reliable for distinguishing functional from structural AKI in this setting. Renal venous Doppler has emerged as a practical method to phenotype congestion. A normal continuous renal venous flow indicates the absence of renal venous hypertension, whereas abnormal waveforms (pulsatile, biphasic, and finally monophasic) indicate progressive congestion. These patterns correlate with impaired diuretic response, faster GFR decline, and higher risks of hospitalization and death, irrespective of the underlying cause of congestion [8, 19]. Thus, when interpreted alongside creatinine changes, renal venous Doppler can provide crucial context: a patient with RSC but improving venous flow and effective natriuresis is likely experiencing a functional, reversible change in GFR, whereas one RSC associated with diuretic resistance and persistent biphasic or monophasic flow likely represents persistent congestion from right-sided HF or volume overload contributing to repetitive renal injury. Such differentiation may guide GDMT and decongestive strategies, pending validation in randomized trials.

Proposed approach to the clinical problem

These insights support the concept of "permissive AKI", in which RSC is tolerated during decongestion or GDMT initiation. In the absence of oliguria, electrolyte disturbances, acidosis, or evidence of tubular injury, these changes should not prompt discontinuation of therapy.

A practical approach (Fig. 1) begins with identifying an RSC ≥ 0.3 mg/dL. If the rise occurs with declining BNP, high urine sodium, and improving renal venous flow, it most likely represents a functional change ("permissive AKI")—therapy should be continued with close monitoring. Conversely, RSC accompanied by stable or rising BNP, hypochloremia [6], low urine sodium (defined as < 50–70 mmol/L after loop diuretic administration and reflecting impaired natriuretic response) [21], abnormal urinary sediment, and persistent biphasic or monophasic venous flow suggest structural kidney injury with unresolved congestion, warranting reassessment of volume status, optimization of RV function, and adjustment of drug dosing. The VEXUS score, which integrates hepatic, portal, and renal venous Doppler, may complement congestion assessment, particularly when renal venous flow is difficult to interpret in advanced CKD, although its incremental value over renal Doppler alone for differentiating RSC has not been established. Importantly, the interpretation of kidney function and the presumed mechanism of AKI should be clearly documented at ICU discharge to ensure continuity of care, allowing the primary team to continue appropriate GDMT and volume management rather than withholding therapy because of RSC.

In conclusion, interpreting kidney function in HF requires nuance beyond KDIGO thresholds. A RSC of 0.3 mg/dL should not automatically be equated with injury. Instead, interpretation should integrate broader hemodynamic and therapeutic context, incorporating higher thresholds (≥ 0.5 mg/dL), renal venous Doppler findings, and spot urine sodium. Recognizing

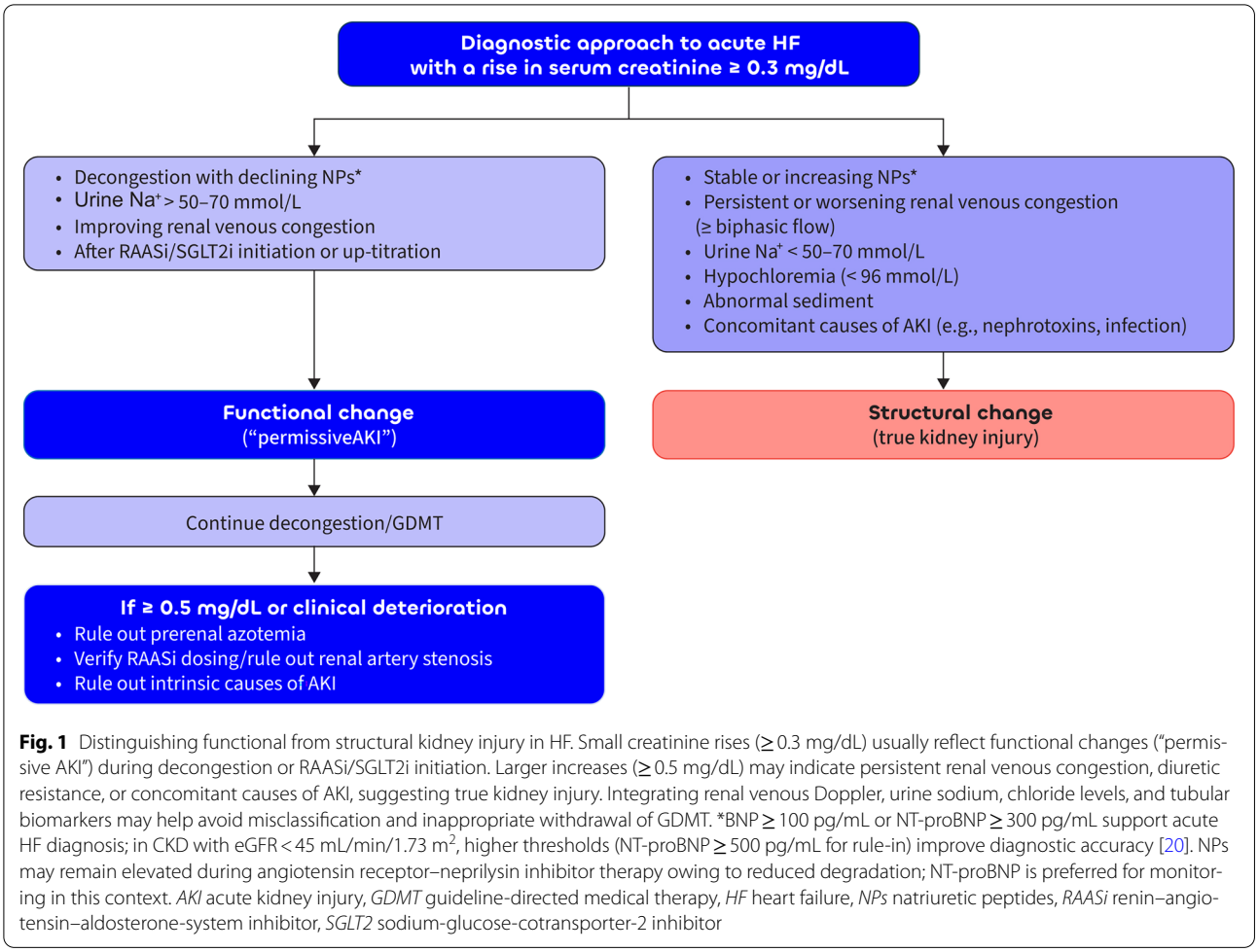
Diagnostic approach to acute HF
with a rise in serum creatinine ≥ 0.3 mg/dL
• Decongestion with declining NPs*
• Urine Na+ > 50–70 mmol/L
• Improving renal venous congestion
• After RAASi/SGLT2i initiation or up-titration
• Stable or increasing NPs*
• Persistent or worsening renal venous congestion (≥ biphasic flow)
• Urine Na+ < 50–70 mmol/L
• Hypochloremia (< 96 mmol/L)
• Abnormal sediment
• Concomitant causes of AKI (e.g., nephrotoxins, infection)
Functional change
("permissiveAKI")
Structural change
(true kidney injury)
Continue decongestion/GDMT
If ≥ 0.5 mg/dL or clinical deterioration
• Rule out prerenal azotemia
• Verify RAASi dosing/rule out renal artery stenosis
• Rule out intrinsic causes of AKI

Fig. 1 Distinguishing functional from structural kidney injury in HF. Small creatinine rises (≥ 0.3 mg/dL) usually reflect functional changes ("permissive AKI") during decongestion or RAASi/SGLT2i initiation. Larger increases (≥ 0.5 mg/dL) may indicate persistent renal venous congestion, diuretic resistance, or concomitant causes of AKI, suggesting true kidney injury. Integrating renal venous Doppler, urine sodium, chloride levels, and tubular biomarkers may help avoid misclassification and inappropriate withdrawal of GDMT. *BNP ≥ 100 pg/mL or NT-proBNP ≥ 300 pg/mL support acute HF diagnosis; in CKD with eGFR < 45 mL/min/1.73 m^2, higher thresholds (NT-proBNP ≥ 500 pg/mL for rule-in) improve diagnostic accuracy [20]. NPs may remain elevated during angiotensin receptor–neprilysin inhibitor therapy owing to reduced degradation; NT-proBNP is preferred for monitoring in this context. *AKI* acute kidney injury, *GDMT* guideline-directed medical therapy, *HF* heart failure, *NPs* natriuretic peptides, *RAASi* renin–angiotensin–aldosterone-system inhibitor, *SGLT2* sodium-glucose-cotransporter-2 inhibitor

permissive creatinine increases as markers of effective therapy rather than parenchymal damage can prevent premature withdrawal of GDMT. Embedding congestion phenotyping and contextual kidney assessment into practice and trial design may ultimately resolve the ongoing challenge of distinguishing functional from true kidney injury across the cardiorenal continuum.

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Declarations

Conflicts of interest
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